REMARKS

Claims 23, 24, and 26-28 are pending in the present application.

Present Claims 23, 24, and 26 relate to crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester produced by:

(1) subjecting N-L-α-aspartyl-L-phenylalanine 1-methyl ester and 3-(3-methoxy-4-hydroxyphenyl)propionaldehyde or a derivative thereof to reductive alkylation in a solvent to obtain N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester; and

(2) crystallizing said N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester,

wherein said reductive alkylation comprises catalytic hydrogenation, and

wherein said derivative thereof is selected from the group consisting of

3-(3-methoxy-4-hydroxyphenyl)-2-propenylaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)propionaldehyde,

3-(3-methoxy-4-protected-hydroxyphenyl)-2-propenylaldehyde, and

acetals derived therefrom.

Present Claims 27 and 28 relate to certain sweetening agents which contain such crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

The cited references contain no disclosure or suggestion of such a crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. Moreover, these references contain no teaching which would instill a reasonable expectation

of success for the presently claimed methods into one of skill in the art. Accordingly, these references cannot affect the patentability of the present claims.

The rejections of: (a) Claims 23, 24, and 26, and (b) Claims 27 and 28, each under 35 U.S.C. § 102(b) over U.S. Patent No. 5,480,668 (Nofre et al) are respectfully traversed.

At column 7, lines 48-51 of Nofre et al, there is found a description showing that the 3,3-dimethylbutyl derivative has been crystallized in the solvent of ethanol/water or acetonitrile. However, this reference does not describe that a series of the compounds can be purified with the same or similar crystallization method and/or with the same solvent. Further, with respect to the compound 18 shown in the Table 1 of Nofre et al, this reference does not describe even the following:

(1) How the compound has been purified (how to purify);

(2) Whether or not the compound can be isolated in the crystalline form; or

(3) Even if the compound exists as a crystalline form.

Since there is no disclosure of crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, this reference cannot anticipate any of Claims 23-26. Moreover, since there is no disclosure of how to purify N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester or whether N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester even exists in the crystalline state, this reference cannot make Claims 23-26 obvious.

The Examiner chooses to disregard the deficiency in the disclosure of Nofre et al and asserts that Applicants have not distinguished the compound disclosed by Nofre et al to be different from the claimed crystalline form. Moreover, in paragraph 11 of paper number 10, the examiner states: "Compounds are distinguished by their atoms and bonds and not by their

method of production. The diffraction peaks are an inherent property of the compound disclosed by Nofre." The Examiner further states, in paragraphs 12 and 14 of paper number 10: "The properties of the compound disclosed by Nofre, including crystallinity and diffraction pattern, are considered by the Examiner to be inherent properties of the compound disclosed by Nofre."

Applicants direct the Examiner's attention to MPEP §2112, which states:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)

The Examiner has clearly failed to provide any reasonable basis in fact and/or technical reasoning to support a determination of inherency. In fact, all the Examiner has done is simply stated his conclusion.

Not only has the Examiner failed to provide any basis in fact or technical reasoning, Applicants note that the Examiner has even failed to make a *prima facie* case of obviousness. When an Examiner maintains that there is an implicit teaching or suggestion in the prior art, "the Examiner should indicate where (page and line or figure) such a teaching or suggestion appears in the prior art." (*Ex parte* Jones, 62 USPQ2d 1206, 1208 (Bd. Pat. App. & Inter. 2001) (**copy enclosed herewith**). However, as stated above, the Examiner has failed to provide a reason, explanation, or specific citation to support his conclusory statements set forth in paragraphs 11-14 of paper number 10. Therefore, the Office has not met the burden necessary to establish a *prima facie* case of obviousness.

Moreover, Applicants respectfully disagree with the conclusions by the Examiner that the properties of the compound disclosed by Nofre et al, including crystallinity and diffraction pattern, are inherent properties of the compound disclosed by Nofre et al. In support of the

proposition that the properties of the inventive compound and the method of crystallization therefor are not inherent to the disclosure of Nofre et al, Applicants **submit herewith** a Declaration of Professor Jerry Atwood ("Atwood Declaration").

As is clearly evident by Appendix A of the Atwood Declaration, Professor Atwood is highly published and has received numerous awards in the field of the present endeavor. From 1985 to 1998, Professor Atwood was Editor of the *Journal of Chemical Crystallography*. In 1999 he was named Consulting Editor for the *Journal of Chemical Crystallography*. He has edited the *Journal of Supramolecular Chemistry* since 2000, and has been Associate Editor of *Chemical Communications* since 1996. From 1992 until 2000, Professor Atwood was editor of *Supramolecular Chemistry*. From 1985 to 1993, he was Regional Editor for the *Journal of Coordination Chemistry*. Professor Atwood is co-Editor of the *Inclusion Compounds* book series (five volumes), *Comprehensive Supramolecular Chemistry* (ten volumes) and the *Encyclopedia of Supramolecular Chemistry* (two volumes). He currently serves on the Editorial Boards of *Crystal Growth & Design*, *Crystal Engineering*, the *New Journal of Chemistry*, *Supramolecular Chemistry*, and the *Journal of Coordination Chemistry*. Professor Atwood has published more than 500 articles in refereed journals, has authored ten patents, and is an expert in the fields of crystal growth, crystal engineering, and polymer chemistry.

As stated in paragraph 10 of the Atwood Declaration, many organic compounds crystallize in more than one form (i.e one organic compound may crystallize in two or more different forms). These forms are not different in the way in which the atoms of the molecule are connected, but rather in the manner in which the molecules relate to each other in the crystalline state. This behavior is referred to as polymorphism. Polymorphs may have very different physical properties such as melting point, dissolution rate, solubility, particle size,

and hygroscopicity (paragraph 11 of the Atwood Declaration). One polymorph may be much more useful for a given purpose than is another polymorph, even though, chemically, the molecules are the same.

In paragraph 13 of the Atwood Declaration, Professor Atwood summarizes that it is *not possible* to predict polymorphism. He further states that once polymorphs have been discovered, it is necessary to describe the methods and conditions of crystallzation that will afford reproducibility. Therefore, it is not sufficient to simply state that a compound is crystallized from a given solvent. Polymorphs may be obtained even from the same solvent under different crystallization conditions. Therefore, the method by which a particular polymorph may reproducibly be obtained is as novel as the polymorph itself (paragraph 13 of the Atwood Declaration).

At this point, Applicants wonder: If one of skill in the art deems the existence of a polymorph and the method by which the polymorph is obtained to be novel and unobvious in view of the art of record, how can one of less than the requisite skill consider it to be anything else?

The present specification discloses the crystallization of the Aspartame derivative N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester. A detailed description of the conditions of crystallization is given. The resulting crystals are defined in terms of their X-ray powder diffraction (XRPD) pattern. As opined by Professor Atwood, "upon reading the Application, one of ordinary skill in the art would understand how to crystallize N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester, and would further know that the desired crystalline compound had been prepared by performing a standard XRPD study." (paragraph 16 of the Atwood Declaration)

With respect to the disclosure of Nofre et al, citing column 7, lines 47-51, Professor

Atwood further opines: "At best, the Nofre '668 Patent teaches a general synthetic method for the production of the compounds appearing in Table 1. In fact, the only synthetic method exemplified in the Nofre '668 Patent is for N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester... Therefore, not only does the Nofre '668 Patent fail to disclose an actual synthetic method for the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester compound, it also falls short of the mark with regard to crystallization." (paragraph 17 of the Atwood Declaration)

Applicants direct the Examiner's attention to paragraph 20 of the Atwood Declaration in which Professor Atwood summarizes the differences between the present invention and the disclosure of Nofre et al. In particular, Professor Atwood summarizes the deficiencies in the disclosure of Nofre et al and why this disclosure does not anticipate and/or render obvious the present invention. For the Examiner's convenience, paragraph 20 of the Atwood Declaration is reproduced below:

> In summary, the teachings of the Nofre '668 Patent at best provides a synthetic method for the production of the N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester molecule, but the crystallization teaching is lacking. Nofre does not teach any crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester. Therefore, based on the teaching of the Nofre '668 Patent, one of ordinary skill in the art would not find crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester to be obvious. It is only the Application that teaches crystallization and the crystal form of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester.

In view of the foregoing, Applicants submit that contrary to the Examiner's assertions, polymorphism is a clear, art-recognized phenomenon, which cannot be predicted in crystalline form or method of making the same. Accordingly, the particular polymorph claimed herein in Claims 23, 24, and 26 is not inherent in the disclosure of Nofre et al, which

clearly is silent with respect to any production method or crystalline form of the claimed N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester. Accordingly, Nofre et al cannot affect the patentability of Claims 23, 24, and 26.

As explained above Claim 23 is fully patentable over Nofre et al. Claims 27 and 28 recite the presence of the crystalline N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester of Claim 23. Thus, Claims 27 and 28 are patentable over Nofre et al for at least the same reasons that Claim 23 is patentable over this reference.

For the foregoing reasons, Nofre et al fails to anticipate and/or render obvious the present invention. As such, these grounds of rejection should be withdrawn.

The rejections of: (a) Claims 1-6, 8, 9, 13-15, 17-22, 30-32, 34, 35, 38, and 39 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al); (b) Claims 7, 10-12, 33, and 36-37 under 35 U.S.C. § 103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al) and U.S. Patent No. 6,077,962 (Prakash et al); and (c) Claim 29 under 35 U.S.C. §103(a) over U.S. Patent No. 5,480,668 (Nofre et al) in view of U.S. Patent No. 5,510,508 (Claude et al) and Solomons (Organic Chemistry 1992), are obviated by the cancellation of the objected to claims.

In the amendment presented herein, Claims 1-22, 25, and 29-39 have been canceled. In so doing, Applicants make no statement regarding the propriety of the aforementioned grounds of rejection. However, it is requested that cancellation of these claims be without prejudice toward the further prosecution of these claim in a continuation and/or divisional application.

An indication that these grounds of rejection have been withdrawn is requested.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Attorney of Record
Registration No. 24,618

Vincent K. Shier, Ph.D.
Registration No. 50,552

22850
(703) 413-3000
Fax #: (703)413-2220
NFO/VKS